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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,183	10/28/2003	David S. Garvey	102258.287 US4	2756

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EXAMINER	
SOROUSH, ALI	
ART UNIT	PAPER NUMBER
1616	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/694,183	GARVEY ET AL.	
	Examiner	Art Unit	
	Ali Soroush	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,36 and 38-46* is/are pending in the application.

4a) Of the above claim(s) *1-34, 37, and 47-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,36 and 38-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response dated 03/14/2007 to Office Action mailed on 02/21/2007 is acknowledged. Examiner acknowledges Applicants species election of the specific disease to be examined as **chronic obstructive pulmonary disease**. Examiner further acknowledges Applicants previous election of Group V (claims 35-46), election of specific phosphodiesterase inhibitor as **Sildenafil**, compound that stimulates endogenous nitric oxide as **L-arginine** in response to previous Office Actions.

Status of the Claims

Claims 35,36, and 38-46 are currently pending examination. Claims 1-34, 37, and 47-63 are drawn to non-elected subject matter and will not be examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35, 36, and 38-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "treating a disease", does not reasonably provide enablement for "preventing a disease". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure

would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention
(2) the state of the prior art
(3) the relative skill of those in the art
(4) the predictability of the art
(5) the breadth of the claims
(6) the amount of direction or guidance provided
(7) the presence or absence of working examples
(8) the quantity of experimentation necessary

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth herein below.

The nature of the invention

The claims are to directed to a method of treating or preventing disease by administering at least one phospodiesterase and at least one compound that stimulates endogenous nitric oxide, elevates levels of endogenous endothelium-derived relaxing factor or is substrate for nitric oxide synthase. Optionally the treatment can comprise an additional vasoactive agent.

The state of the prior art

Harrison et al. teaches, "Spontaneous preterm labor during pregnancy remains an enormous, and apparently increasing problem confronting the medical community." (See column 1, Lines 25-27). Drumm et al. (US Patent 5,602,110, Published 02/11/1997) teaches, "Cystic fibrosis ('CF') is a congenital disease characterized by abnormal fluid and solute balance across the epithelial cells of several organs." (See column 1, Lines 26-28). Therefore, from the examples of Harrison et al. and Drumm et

al. one can clearly see that "prevention of a disease" is not enabled. In the case of spontaneous preterm labor a medical practitioner could not anticipate such an occurrence and therefore would not be able to prevent preterm labor by administration of at least one phospodiesterase and at least one compound that stimulates endogenous nitric oxide, elevates levels of endogenous endothelium-derived relaxing factor or is substrate for nitric oxide synthase and optionally vasoactive agent. In the case of cystic fibrosis, a genetic disease that also cannot be prevented by the instantly claimed method because cystic fibrosis is a genetic disease that expresses its symptoms almost immediately following birth.

The breadth of the claims / The amount of direction or guidance provided

Applicant's claim is directed to a wide variety of disease states, which encompass every physiological organ including lungs, heart, kidneys, vasculature, eyes, etc. However, the applicant does not give working examples to permit an artisan of ordinary skill to practice the instantly claimed method with these varied disease states.

The quantity of experimentation necessary

Applicant's specification does not provide guidance as to how such a method is to be applied in each case of the disease state. An artisan of ordinary skill in the art would not be able to practice the instantly claimed method because the artisan would need to know what concentrations would be effective in the different organs or what optional agents would be need in treatment of the different disease states. Therefore,

an artisan of ordinary skill in the art would have to perform undue experimentation to practice the instantly claimed invention.

Therefore, for the aforementioned reasons, the Applicant is not enabled for prevention of a disease since undue experimentation would be required to use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 35, 39, and 41-44 rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Harrison et al. (US Patent 5,508045, Published 04/16/1996).

Harrison et al. teaches, "A method for control, management and inhibition of preterm labor by providing to a pregnant woman a donor of nitric acid." (See abstract). Harrison et al. further teaches, "An additional preferred embodiment of the invention is a labor retarding composition comprising L-arginine, metabolic precursor thereof, analogues thereof, or mixtures thereof, along with a phosphodiesterase inhibitor such as papaverine or zaprinast." (See column 23, Lines 24-28). "Nitric oxide is

produced in vascular endothelial cells by nitric oxide synthase and seems to mediate vascular smooth muscle relaxation by increasing levels of cGMP." (See column 3, Lines 18-20). "Nitric oxide is synthesized from amino acid L-arginine by the nitric oxide synthase (NOS)." (See column 3, Lines 11-12). "The composition in accordance with this method maybe administered orally, transdermally, subcutaneously, intravaneously, intraperitoneally, intramuscularly, intranasally, rectally or intravaginally." (See column 24, Lines 36-39). For the foregoing reasons the instantly claimed method of treating or preventing disease by administering at least one phospodiesterase and at least one compound that stimulates endogenous nitric oxide, elevates levels of endogenous endothelium-derived relaxing factor or is substrate for nitric oxide synthase is anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue; and resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 35, 36, 39, and 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson et al. (WO 95/09636, Published 04/13/1995).

Applicant Claims

Applicant claims a method of treating or preventing disease by administering at least one phospodiesterase and at least one compound that stimulates endogenous nitric oxide, elevates levels of endogenous endothelium-derived relaxing factor or is substrate for nitric oxide synthase.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Lawson et al. teaches, "This invention provides a method of selectively decreasing pulmonary vascular resistance in a subject by administering endobronchially a drug chosen from cAMP analogs, cGMP analogs, phosphodiesterase inhibitors, nitric oxide precursors, nitric oxide donors, and nitric oxide analogs." (See abstract). "This invention also provides for a method of treating a pulmonary condition in a subject which comprises administering endotracheally or endobronchially an effective amount of a drug selected from the group consisting of cyclic nucleotides, phosphodiesterase inhibitors, nitiric oxide precursors, nitric oxide donors, and nitric oxide analogs, thereby decreasing pulmonary vascular resistance.In an embodiment of this method the pulmonary condition is selected from the group consisting of primary pulmonary hypertension, chronic obstructive pulmonary disease ..." (See page 13, Lines 10-20). "In another embodiment the administering comprises inhaling the drug in an aerosol

form." (See page 14, Lines 1-2). Lawson et al. further teaches, "Phosphodiesterase (PDE) inhibitors are commonly categorized according to five families." (See page 16, Lines 14-15). Lawson et al. gives zaprinsat and dipyridamole as examples of Family V of phosphodiesterase inhibitors. (See page 17, Line 11). "In an embodiment, the nitric oxide precursor is L-arginine." (See page 17, Lines 22-23).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Lawson et al. does not anticipate the instant invention since one cannot immediately envisage the utilization of both a phosphodiester inhibitor and nitric oxide precursor, i.e. L-arginine, in one treatment session of a patient in need thereof.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

Although, Lawson et al. does not anticipate the instant invention it would have been obvious to one of ordinary skill in the art at the time of the presently claimed invention to administer both a phosphodiesterase inhibitor and L-arginine to a patient in need thereof. One would have been motivated to do this in order to provide an additive effect of both compounds in treating chronic obstructive disease. Thus, if one desired to provide a treatment of chronic obstructive disease a skilled artisan would utilize a phosphodiesterase inhibitor and L-arginine, a substrate of nitric oxide synthase, and other methods that would provide for vascular smooth muscle relaxation. For the foregoing reasons the instantly claimed method of treatment or prevention of a disease is made obvious.

2. Claims 38 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson et al. (WO 95/09636, Published 04/13/1995) in view of Terrett et al. (Sildenafil (Viagra™), a Potent and Selective inhibitor of Type 5 cGMP Phosphodiaesterase with Utility for the Treatment of Male Erectile Dysfunction, Published 08/06/1996).

Applicant Claims

Applicant claims a method of treating or preventing disease by administering at least one phospodiesterase, i.e. Sildenafil, and at least one compound that stimulates endogenous nitric oxide, elevates levels of endogenous endothelium-derived relaxing factor or is substrate for nitric oxide synthase.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Lawson et al. are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Lawson et al. does not teach the instant phosphodiester inhibitor sildenafil. Terrett et al. cures this deficiency.

Terrett et al. teaches, Sidenafil to be a "potent and selective inhibitor of type 5 cGMP phosphodiesterase ..." (See title). Terrett et al. further teaches that zaprinast "was one of the first type 5 PDE inhibitors to be reported, albeit only weakly active and a poorly selective" drug. (See page 1819, Lines 23-24).

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

Although, Lawson et al. does not anticipate the instant invention it would have been obvious to one of ordinary skill in the art at the time of the presently claimed invention to utilize sildenafil in place of zaprinast. Therefore, the use of sildenafil over zaprinast would impart a better selectivity and stronger activity to a composition used in treating a disease. It is note by the examiner that Terrett et al. teaches the use of sildenafil for male erectile dysfunction. However, because sildenafil is taught to be a type 5 phosphidiesterase inhibitor it would have been obvious to one skilled in the art that the compound could be equally useful in treatment of chronic obstructive pulmonary disease. One would have reasonably expected that sildenafil would also be useful in the method since Lawson et al. teaches that PDE-5 inhibitors in general treat chronic obstructive pulmonary disease and Terrett et al. discloses sildenfil to have the same function of being a type 5 inhibitor of phospdiesterase. For the foregoing reasons the instantly claimed method of treatment or prevention of a disease is made obvious.

3. Claims 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson et al. (WO 95/09636, Published 04/13/1995) in view of Cuneo et al. (Pharmacodynamics and Pharmacokinetics of Esmolol, A short Acting β-Blocking Agent, in Children, Published 1994).

Applicant Claims

Applicant claims a method of treating or preventing disease by administering at least one phospodiesterase and at least one compound that stimulates endogenous nitric oxide, elevates levels of endogenous endothelium-derived relaxing factor or is

substrate for nitric oxide synthase. Optionally, the method comprises administering a vasoactive agent such as a β-blocker.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Lawson et al. are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Lawson et al. does not teach a vasoactive agent. Cuneo et al. cures this deficiency.

Cuneo et al. teaches, "Esmolol, a short acting intravenous cardioselective β-blocking agent ..." (See page 296, Line 1). "Esmolol has been used in a variety of clinical situations. It has been safely given to patients with chronic obstructive pulmonary disease, causing effective β-blockade without respiratory compromise." (See page 300, Column 2, Lines 28-32).

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

Although, Lawson et al. does not anticipate the instant invention it would have been obvious to one of ordinary skill in the art at the time of the presently claimed invention to utilize esmolol in addition to the phosphodiesterase inhibitor and L-arginine. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Therefore, one would have been motivated

to further use esmolol since Cuneo et al. teaches esmolol is used to treat chronic obstructive pulmonary disease in order to provide an additive effect in treating chronic obstructive disease. Thus, if one desired to provide a treatment of chronic obstructive disease a skilled artisan would utilize a phosphodiesterase inhibitor and L-arginine, a substrate of nitric oxide synthase, and a β-blocking agent that would provide for vascular smooth muscle relaxation. For the foregoing reasons the instantly claimed method of treatment or prevention of a disease is made obvious.

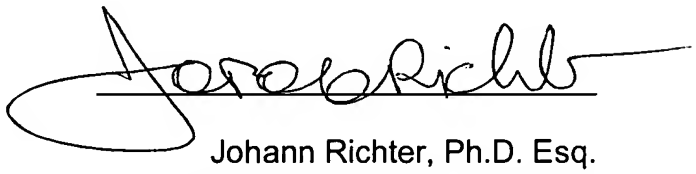
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ali Soroush whose telephone number is (571) 272-9925. The examiner can normally be reached on Monday through Thursday 8:30am to 5:00pm E.S.T.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ali Soroush
Patent Examiner
Art Unit: 1616



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